REMARKS/ARGUMENTS

With this response, claims 1-8, 14-17, 21-26, 35-38 and 51-58 are pending. Claims 9-13, 18-20, 31-34, and 39-41 are withdrawn. Claims 27-30, 42-50, and 58-62 are cancelled. The Examiner's rejections are addressed in the order presented in the Office Action dated August 10, 2006. New claim 63 is added. Support for this claim is found throughout the specification, for example, at Example 3, page 52. This amendment adds no new matter.

Rejections under 35 U.S.C. §103(a)

A. Introduction

Various combinations of claims are rejected for alleged obviousness in view of various combinations of references. Applicants respectfully traverse the rejections.

The Office Action has not established a case of *prima facie* obviousness. As the Examiner knows, in order to establish a case of *prima facie* obviousness, the rejection must meet three basic criteria:

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). M.P.E.P. §§ 706.02(j) and 2143.

The references cited by the Office Action fail to provide a reasonable expectation of success in practicing the invention and fail to provide a motivation for the combination of the references. In addition, the references cited by the Office Action fail to provide all the elements of the rejected claims. Therefore, Applicants respectfully traverse the rejections.

In response to the most recent Office Action, Applicants make the following remarks, which are applicable to all the cited combinations of references.

First, the Office Action continues to misinterpret the disclosure of Weber *et al.* Weber *et al.* discloses a solution to a particular problem, tiazofurin toxicity and development of resistance after adminstration to treat cancer. Weber *et al.* solves this problem by sequential administration of a high dose of tiazofurin followed by low doses of ribavirin. Weber *et al.* selected ribavirin for administration with tiazofurin because the two drugs inhibit the same enzyme, IMPDH. The sequential administration of tiazofurin and ribavirin is the only drug combination disclosed by Weber *et al.* IN contrast, the claimed invention is administration of an inhibitor of IMPDH in combination with a different class of drug, *e.g.*, an inhibitor of α-tubulin polymerization, an inhibitor of de novo purine biosynthesis, or an antagonist of a G-protein coupled receptor, generically referred to as agents that inhibit a cellular process regulated by GTP or ATP. Weber *et al.* does not disclose administration of an IMPDH inhibitor with any of these classes of drugs.

Although Weber *et al.* discloses only administration of two IMPDH inhibitors, the Office Action appears to take a sentence at column 2 lines 8-11 to mean administration of tiazofurin with any second compound. Even if this interpretation were correct, Weber *et al.* provides no motivation for those of skill to select the claimed drug classes or specific drugs from the large number of chemotherapeutic agents for administration with an IMPDH inhibitor. Weber *et al.* narrow the range of selectable compounds by disclosing administration of two compounds that both inhibit IMPDH, tiazofurin followed by ribavirin. No advantage or expectation of success is provided to select a second agent that does not replicate tiazofurin's inhibition of IMPDH activity.

Second, the Office Action at page 12 asserts that the obviousness rejection is proper "since one of ordinary skill in the art would have expected greater efficacy with a combination of agents having different mechanisms of action over a combination of agents having the same mechanism of action." No reference is cited to provide support for this assertion. In response, Applicants respectfully point to MPEP 2144.02, which states that ". . . when an examiner relies on a scientific theory, evidentiary support for the existence and meaning of that theory must be provided." *Citing In re Grose*, 201 USPQ 57 (CCPA 1979). Applicants

request that, should another Office Action issue, the Examiner specifically point out the scientific theory relied on and evidence of that theory.

B. Rejection of claims 1-8

Claims 1-8 are rejected as obvious over Markovic *et al.*, US Patent No. 5,358,855 in view of Weber *et al.*, US Patent No. 5,405,837, further in view of Chen *et al, Jap. J. Cancer* (1990); and further in view of Leoni *et al., J. Nat'l Cancer Inst.* (2000).

Claims 1-8 are directed to methods of treating cancer by administering to a subject a combination of an inhibitor of the inosine monophosphate dehydrogenase (IMPDH) enzyme and an agent that inhibits a cellular process regulated by GTP or ATP. Dependent claims 2-8 are all directed to use of a specific class of agents that inhibit a cellular process inhibited by GTP or ATP, *i.e.*, inhibitors of tubulin polymerization. The cited references (discussed below) do not provide all the elements of the claimed methods. Moreover, Examples 1 and 2 of the specification provide evidence that, at a minimum, the subgenus of methods encompassed by claims 2-8 have unexpected benefits, not known to those of skill until the filing of this application.

Markovic *et al.*, US Patent No. 5,358,855

Markovic *et al.* disclose a role for IMPDH inhibitors as cancer chemotherapeutics. Applicants agree with the Office Action at page 4, that Markovic *et al.* do not teach the administration of IMPDH inhibitors in combination with other cancer chemotherapeutics as a treatment for cancer.

Weber et al., US Patent No. 5,405,837

Weber *et al.* teach treatment of cancer by administering two compounds that inhibit activity of the IMPDH enzyme: tiazofurin and ribavirin. No other chemotherapeutic compounds are taught or suggested for administration with tiazofurin and the dosages are

tailored to the patient by monitoring the GTP concentration and the activity of the IMPDH enzyme.

Chen *et al, Jap. J. Cancer* (1990)

Chen *et al.* disclose circumstances under which mizoribine, an IMPDH inhibitor, enhances the growth of tumor cells. Chen *et al.* developed a cost-effective version of the murine subrenal capsule assay (SRCA), using wild-type mice, rather than expensive nude or SCID mice. Chen *et al.* administered mizoribine to trying to inactivate the immune system of the wild type mice thereby allowing growth of the tumor cells for further study. At low mizoribine doses, the immune system was not inactivated and the non-self tumor cells did not grow because of immune system action. At high mizoribine levels, the host mouse immune system was inactivated and the growth of tumor cells actually increased. In addition, the authors also noted that the high mizoribine dose inactivated the immune system and was toxic to the host mice.

Leoni *et al., J. Nat'l Cancer Inst.* (2000)

Leoni *et al.* disclose that indanocine inhibits α-tubulin polymerization and has antiproliferative activity against cell lines derived from human cancers, including multi-drug resistant cell lines. Leoni *et al.* did not test other chemotherapeutic agents alone or in combination with indanocie.

The cited references, alone or together, do not teach or suggest all the elements of the claimed invention and do not provide a motivation for their combination to arrive at the claimed invention. According to the Office Action, Weber *et al.* teach generally treatment of cancer comprising administration of tiazofurin with another chemotherapeutic agent. This is incorrect. Tiazofurin is an IMPDH inhibitor. Weber *et al.* address a problem of toxic reaction or resistance to tiazofurin administration by administering a second IMPDH inhibitor, *i.e.* ribavirin,. The use of a second chemotherapeutic agent with a different mechanism of action, *e.g.*, an agent that inhibits a cellular process regulated by GTP, such as tubulin polymerization, de novo purine

metabolism, activity of a GPCR protein, or that inhibits DNA replication is not disclosed or suggested by Weber *et al.* Weber *et al.* does not disclose or suggest combining tiazofurin with agents that do not affect IMPDH activity.

According to the Office Action, Chen *et al.* teaches that mizoribine, an IMPDH inhibitor, effectively reduces the size of tumors. The Office Action points to figure 2 of Chen *et al.* Applicants assert that figure 2 of Chen *et al.* shows that administration of mizoribine has either little effect on tumor size or actually appears to increase tumor size, as compared to controls. The most striking effect of mizoribine is shown at 400 mg administration level, where mizoribine appeared to greatly decrease the body weight of the mice, while increasing the tumor size. Thus, Chen *et al.* actually teach away from combination of mizoribine with other toxic chemotherapeutic agents, as taught by Weber *et al.* and allegedly by the other cited references.

Markovic *et al.* teaches only an assay for IMPDH activity and that tiazofurin is an inhibitor of the enzyme. Markovic *et al.* provides no motivation to combine tiazofurin or any other IMPDH inhibitor with a different class of chemotherapeutic agent for cancer treatment. Leoni *et al.* disclose anti-proliferative properties of indanocine, but do not teach or suggest combination of this tubulin polymerization inhibitor with drugs that have a different mechanism of action. Thus, Markovic *et al.* and Leoni *et al.*, fail to correct the deficiencies of Weber *et al.* and Chen *et al.* Therefore, no motivation for combination or expectation of successful results is found in the cited references.

The specification also discloses that treatment of cancer cells with an IMPDH inhibitor and an agent that inhibits α-tubulin polymerization unexpectedly increases cancer cell death. *See,* specification, *e.g.*, at page 23, line 4 through page 25, line 11. A specific example is found at Example 2, page 51, line 31 through page 52 line 11 and Fig. 2. The example shows the results of treating chronic lymphocytic leukemia (CLL) cells with either indanocine, mizoribine, or a combination of indanocine and mizoribine. Without any treatment 65% of the CLL cells were viable 24 hours after the start of the experiment. Treatment with 1 μM indanocine resulted in death of more than half of the surviving CLL cells (24% viability). Treatment with 1 μM or 10 μM mizoribine resulted in only a negligible decrease in CLL cell viability (55% or 45%,

respectively). However, when indanocine and mizoribine (both concentrations) were administered to the CLL cells, the cell viability unexpectedly dropped to less than 10% of the surviving cells. These surprising results support the non-obviousness of the claimed methods.

C. Rejection of claims 14-17

Claims 14-17 are rejected as obvious over Markovic *et al.*, US Patent No. 5,358,855 in view of Weber *et al.*, US Patent No. 5,405,837, further in view of Chen *et al, Jap. J. Cancer* (1990); and further in view of Ucken *et al., Blood* (1998).

Claims 14-17 depend from claim 1 and are directed to methods to treat cancer by administering to a subject a combination of an IMPDH inhibitor and a precursor or prodrug of 9-beta-D-arabinofuranosylguanine 5'-triphosphate (Ara-GTP). Markovic *et al.*, Weber *et al.*, and Chen *et al*, are discussed above. Ucken *et al.* is discussed below. The cited references do not provide all the elements of the claimed methods. Moreover, the specification at page 25, lines 13-32 discloses improved results in killing cancer cell with the combination of an IMPDH inhibitor and a precursor or prodrug of Ara-GTP.

Ucken *et al., Blood* (1998)

According to the Office Action, Ucken *et al.* disclose that Ara-G is selectively cytotoxic for T-cell lines and T-lineage leukemic cells.

The cited references, alone or together, do not teach or suggest all the elements of the claimed invention and do not provide a motivation for their combination to arrive at the claimed invention. Applicants refer the Examiner to section B, above, for discussion of the deficiencies of Weber *et al.* and Chen *et al.*, neither of which contributes the required elements of the claims and motivation to combine the cited references. The other cited references, Markovic *et al.* and Ucken *et al.* fail to correct the deficiencies of Weber *et al.* and Chen *et al.*

D. Rejection of claims 21-26

Claims 21-26 are rejected as obvious over Markovic *et al.*, US Patent No. 5,358,855 in view of Weber *et al.*, US Patent No. 5,405,837, further in view of Chen *et al, Jap. J. Cancer* (1990); and Carrera *et al.*, US Patent No. 5,840,505.

Claims 21-26 depend from claim 1 and are directed to methods to treat cancer by administering a combination of an IMPDH inhibitor and an agent that inhibits and an inhibitor of the de novo pathway of purine biosynthesis. Markovic *et al.*, Weber *et al.*, and Chen *et al*, are discussed above. Carrera *et al.* is discussed below.

Carrera *et al., Blood* (1998)

According to the Office Action, Carrera *et al.* disclose that L-alanosine, an inhibitor of purine biosynthesis, can be used to treat cancer cells, including cancer cells that lack MTAse activity.

The cited references, alone or together, do not teach or suggest all the elements of the claimed invention and do not provide a motivation for their combination to arrive at the claimed invention. Applicants refer the Examiner to section B, above, for discussion of the deficiencies of Weber *et al.* and Chen *et al.*, neither of which contributes the required elements of the claims and motivation to combine the cited references. The other cited references, Markovic *et al.* and Carrera *et al.* fail to correct the deficiencies of Weber *et al.* and Chen *et al.*

Moreover, at page 26, line1 through page 27, line 22, the specification discloses treatment of cancer using an IMPDH inhibitor in combination with an inhibitor of de novo purine biosynthesis. A specific example is found at Example 4, page 52, line 24 through page 53 line 4 and Fig. 4. The example shows that for lung cancer cells (A569 cells) the IC_{50} and IC_{90} of L-alanosine unexpectedly decrease with increasing amounts of mizoribine-base. Without any mizoribine present, the IC_{50} of L-alanosine is 5 μM and the IC_{90} of L-alanosine is 20 μM. With 5 μM mizoribine present, the IC_{50} of L-alanosine drops to 0.5 μM and the IC_{90} drops to of L-alanosine is 9 μM. With 25 μM mizoribine present, the IC_{50} of L-alanosine is 0.25 μM and the

IC_{90} of L-alanosine is 6 μM. With 50 μM mizoribine present, the IC_{50} of L-alanosine decreases to 0.15 μM and the IC_{90} of L-alanosine decreases to 4 μM. These surprising results support the non-obviousness of the claimed methods.

E. Rejection of claims 35-38

Claims 35-38 are rejected as obvious over Markovic *et al.*, US Patent No. 5,358,855 in view of Weber *et al.*, US Patent No. 5,405,837, further in view of Chen *et al, Jap. J. Cancer* (1990); and Weers *et al.*, US Patent Application No. 2003/0003057.

Claims 35-38 are directed to methods to treat cancer by administering to a subject a combination of an inhibitor of the IMPDH enzyme and an agent that inhibits a cellular process regulated by GTP that is an antagonist of a G-protein coupled receptor (GPCR). Markovic *et al.*, Weber *et al.*, and Chen *et al*, are discussed above. Weers *et al.* is discussed below.

Weers *et al., Blood* (1998)

According to the Office Action, Weers *et al.* disclose administration of inhaled leuprolide to treat a variety of conditions. Weers *et al.* does not suggest administration of leuprolide with another chemotherapeutic agent.

The cited references, alone or together, do not teach or suggest all the elements of the claimed invention and do not provide a motivation for their combination to arrive at the claimed invention. Applicants refer the Examiner to section B, above, for discussion of the deficiencies of Weber *et al.* and Chen *et al.*, neither of which contributes the required elements of the claims and motivation to combine the cited references. The other cited references, Markovic *et al.* and Weers *et al.* fail to correct the deficiencies of Weber *et al.* and Chen *et al.*

At page 34, line 4 through page 36, line 11, the specification discloses treatment of cancer using an IMPDH inhibitor in combination with a GPCR antagonist. GPCR activity is increased in some cancer cells. GPCR proteins act by regulating intracellular signal transduction pathways. Applicants presented with the last response Exhibit A, Lee *et al.*, *Proc. Nat'l Acad.*

USA 103:1828-1833 (2006), as evidence that IMPDH inhibitors can act synergistically with regulators of signal transduction pathways. Applicants maintain the related arguments but do not repeat them here.

F. Rejection of claims 51-58

Claims 51-58 are rejected as obvious over Markovic *et al.*, US Patent No. 5,358,855 in view of Weber *et al.*, US Patent No. 5,405,837, and Chen *et al, Jap. J. Cancer* (1990).

Claims 51-58 are directed to methods to treat cancer by administering to a subject mizoribine or a related compound so that the plasma level of the compound is maintained between 0.5 and 50 micromolar for between 6 and 72 hours. Markovic *et al.*, Weber *et al.*, and Chen *et al*, are discussed above. The references also fail to render obvious new claim 63, which depends form claim 51 and is directed to treatment of an MTAse deficient cancer.

The cited references, alone or together, do not teach or suggest all the elements of the claimed invention and do not provide a motivation for their combination to arrive at the claimed invention. The Office Action appears to rely on Weber *et al.* for many of the claim elements and for the alleged motivation to combine the references. According to the Office Action, Weber *et al.* teach administration of tiazofurin and ribavirin greater than 4,400 mg/m^2 or in a range between 1100-3300 mg/m^2. Weber *et al.* teach that the most effective dosage regime against cancer combines two IMPDH inhibitors: tiazofurin and ribavirin. Weber *et al.* teaches that daily infusion of tiazofurin can be toxic or can lead to resistance by the cancer. Column 2, lines 6-8. Weber *et al.* also teaches that ribavirin is less effective when administered alone. Column 1, lines 53-56. Therefore, Weber *et al.* provide no motivation to administer a single IMPDH inhibitor for treatment of cancer. At Example 3, page 52, Applicants provide experimental evidence that continual exposure of cancer cells to mizoribine for time periods between 24 and 72 hours decreases the IC_{50} of the drug up to ten fold. These surprising results support the non-obviousness of the claimed methods.

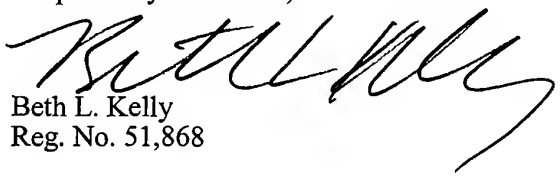
In view of the above arguments and remarks, withdrawal of the rejections for alleged obviousness is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



Beth L. Kelly
Reg. No. 51,868

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 415-576-0200
Fax: 415-576-0300
Attachments
BLK:ds
60962428 v1